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Peritoneal dialysate volume determined by indicator dilution measurements

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Peritoneal dialysate volume determined by indicator dilution measurements. Dialysate volume was simultaneously determined by two different indicator dilution techniques as a function of dwell time in a rabbit model of peritoneal dialysis using isotonic, hypertonic and hypotonic solutions. After a single injection of a large molecular weight index solute (SIIS) to the dialysis solution at a known concentration, the first indicator dilution technique determined dialysate volume by the change in the index solute concentration. In the second technique, dialysate volume was determined after multiple injections of a different index solute (MIIS) by measuring the change in concentration of the index solute two minutes after its injection into the dialysis solution. The volumes determined by SIIS were similar during isotonic, but larger during both hypertonic and hypotonic exchanges, than those determined by MIIS. Drained volume was dependent upon the peritoneal catheter used, was not different from that determined by MIIS, but was significantly smaller than that determined by SIIS. The present results suggest that systematic errors in volume measurements when using indicator dilution result from the loss of the index solute from the peritoneal cavity and are greater for SIIS than for MIIS. A model for fluid transfer during peritoneal dialysis showed that dialysate volumes determined by SIIS were useful, however, when estimating the rate of fluid movement across the peritoneal membrane.

The most common methods for determining peritoneal dialysate volume are based on indicator dilution techniques since they can be easily performed and may be readily applied in the clinic. Such techniques are especially advantageous since they permit the determination of dialysate volume as a function of dwell time during an exchange. The indicator dilution technique that has been conventionally employed uses a single injection of the index solute (SIIS) into the dialysis solution, with the subsequent determination of dialysate volume by measuring the change in the index solute concentration [1–6]. The molecular properties of the index solute do not appear to be important since radiolabeled autologous proteins [1], dextran 70 [2], and albumin [5, 6] have all been successfully used. As discussed recently [6, 7], one problem with this approach results from not properly accounting for the loss of the index solute from the peritoneal cavity. Previous investigators have attempted to correct for index solute loss by accounting for the amount appearing in plasma [2, 8]. Recent work has shown, however, that drained volumes from the peritoneal cavity, even with corrections for residual volume, do not agree with these computed volumes [5–7].

In the present work two different methods for determining dialysate volume using indicator dilution were tested in a rabbit model of peritoneal dialysis using isotonic, hypertonic and hypotonic solutions. In addition to the conventional approach described above (SIIS), dialysate volume was simultaneously determined after multiple injections of a different index solute (MIIS) by the concentration change two minutes after index solute injection. Furthermore, the separate contributions of fluid movement either across the peritoneal membrane or through alternative pathways (such as into the lymphatics or adjacent tissue spaces) were estimated using these volume determinations.

Methods

Experimental

Male New Zealand White rabbits weighing between 2.2 and 3.8 kg were fasted overnight and anesthetized with halothane prior to the experiment. Catheters were placed in the jugular vein and carotid artery for infusing solutions and blood sampling, respectively. Both catheters were exteriorized by threading them subcutaneously to an incision in the back of the neck. This procedure allowed the experimenter unrestricted access to the catheters without perturbing the rabbit during the course of the experiment.

A one cm incision in the skin and through the first layer of muscle of the right flank region was required for trocar insertion of the peritoneal catheter. Two different types of peritoneal catheters were used. The first (catheter A) was as described previously [4], a straight 20 cm long silicon tube with approximately 80 holes. The second type (catheter B) was longer and shaped in a serpentine form so that its total length of insertion into the peritoneal space was approximately 40 cm. Catheter B contained considerably more surface area in contact with the dialysis solution and therefore permitted more rapid injection and removal of solutions. This design also kept the catheter in a stable position adjacent to the parietal peritoneum so that it was less likely to be dislocated by movement of the bowel.

After catheter placement, the rabbit was given pure oxygen until conscious. A 60 minute washout exchange of the peritoneal cavity (40 ml/kg) using Normosol R (Abbott Laboratories, North Chicago, Illinois, USA) was then performed. Normosol

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R solutions have a pH of approximately 6.8, and one liter of this solution contains: Na^+, 140 mEq; K^+, 5 mEq; Mg^{2+}, 3 mEq; Cl^-, 98 mEq; acetate, 27 mEq; gluconate, 23 mEq. At the beginning of the washout exchange a constant intravenous infusion was started of 0.45% NaCl and 2.5% dextrose at 20 ml/hr to replace estimated insensible fluid losses. At the end of the washout exchange the peritoneal cavity was drained by gravity as completely as possible. During the experiments the rabbits were allowed to move freely inside their cages with the line to the peritoneal catheter disconnected and sealed between samplings.

Sixteen rabbits underwent an experimental exchange with an isotonic dialysis solution (Normosol R plus 0.5% dextrose). With eight rabbits a hypertonic (Normosol R plus 7% dextrose) and with five a hypotonic (distilled water) exchange followed the isotonic one. All exchanges were scaled to body weight (40 ml/kg).

The protocol for measuring dialysate volume was identical during all exchanges. Dextran T2000 (2×10^6 daltons, 0.1 to 0.3 mg/ml, Sigma Chemical Co., St. Louis, Missouri, USA) was added to the dialysis solution as a marker for calculating dialysate volume using the SIIS method. Blood and dialysate samples were taken at 0, 15, 30, 45, 60, 90 and 120 minutes after the dialysis solution was completely infused. The dialysate samples were used to determine the concentration of both dextran T2000 and the Evans blue-albumin complex. Immediately following the removal of dialysate samples at 0, 15, 45, 90 and 120 minutes, an equal volume of the dialysis solution under evaluation containing Evans blue (0.25 mg/ml, Fisher Scientific Co., Tustin, California, USA) and bovine albumin (5 mg/ml, Sigma) was rapidly injected into the peritoneal cavity. In these proportions Evans blue is completely bound to albumin [9], and this solute is referred to as Evans blue-albumin complex. The dialysis solution was then mixed by repeated aspiration and injection of solution for two minutes. Another sample of dialysate was then taken for determining the dilution of the newly injected dye. An equal volume of the dialysis solution under evaluation was returned to the peritoneal cavity immediately after this sample. After samples were taken at a dwell time of 120 minutes, the peritoneal cavity was again drained by gravity as completely as possible. Depending upon the circumstance, either a hypertonic or hypotonic exchange was then performed.

After drainage of the peritoneal cavity following the hypertonic or hypotonic exchange, the animals were sacrificed by a barbiturate overdose. The intraperitoneal residual volume remaining after catheter drainage was then measured by the following procedure. The peritoneal cavity was opened by first performing a midline incision in the skin of the abdominal wall with the rabbit in the supine position. The skin was elevated with forceps, and the entire abdominal wall was cut along the midline with scissors. This two step procedure caused minimal contamination of peritoneal contents since only the skin vessels bled. The opening into the peritoneal cavity was stretched by bilateral forceps traction and the intestines were taken out manually. Any fluid present was then aspirated with a syringe and measured to the nearest ml.

Three additional rabbits underwent a simplified protocol to assess the degree of mixing of Evans blue-albumin complex following its injection into isotonic peritoneal dialysis solution. Following the placement of the peritoneal catheter (catheter B), a 60 minute washout exchange using Normosol R was performed. Following drainage by gravity of the peritoneal cavity, an isotonic exchange was performed. Five ml of isotonic dialysis solution containing Evans blue and albumin were then rapidly injected into the peritoneal cavity. Samples were taken just prior to the injection and 1/2, 1, 2, 5 and 10 minutes after the injection. Throughout the 10 minute interval the dialysis solution was continuously mixed by repeated aspiration and injection of solution. A combined total of 10 different determinations were performed in these three animals.

Solution osmolalities were measured by osmometry (Osmette A, Model 5002, Precision Systems Inc., Sudbury, Massachusetts, USA). The concentration of dextran T2000 was determined by gel permeation chromatography as described previously [4]. The concentration of Evans blue-albumin complex was determined spectrophotometrically at a wavelength of 612 nm (Gilford Spectrophotometer, Model 300N, Oberlin, Ohio, USA).

Calculations

Dialysate volumes were calculated by indicator dilution using either the dextran T2000 or Evans blue-albumin complex concentrations, assuming there was no loss of index solute from the peritoneal cavity. For dextran T2000, the volume of dialysis solution in the peritoneal cavity at sampling time t_2 was determined from the volume at the previous sampling time t_1 by using the following mass balance relationship:

$$V_{T2000}(t_2) = C_{T2000}(t_1)V_{T2000}(t_1)/C_{T2000}(t_2) \quad (1)$$

The initial volume was assumed to be the infused volume. Thus, the volumes determined using dextran T2000 are by the SIIS method.

The volume of dialysis solution in the peritoneal cavity was also determined using the Evans blue-albumin complex concentrations at each sampling time t by

$$V_{EB}(t) = \frac{v(C_s - C_i)}{C_f - C_i} \quad (2)$$

where v is the volume of Evans blue-albumin complex stock solution of concentration C_s that was added to the peritoneal cavity at time t. The value of C_i is the concentration just prior to addition of stock solution. The value of C_f is either the concentration two minutes after index solute injection or alternatively the concentration at different sampling times in the experiments assessing the mixing of newly injected dye. The value of C_s was determined for each exchange by diluting v ml of the stock Evans blue-albumin complex solution to 100 ml by using the dialysis solution under evaluation. Dialysate volumes determined using the Evans blue-albumin complex concentration are, therefore, by the MIIS method.

The interpretation of these different volume estimates is clarified by a model of fluid transfer during peritoneal dialysis that is mathematically described in the Appendix. The essential features of this model are shown in Figure 1. Fluid movement into and out of the peritoneal cavity is postulated to occur by two different routes. Because of hydrostatic and osmotic forces between plasma and peritoneal dialysate, fluid movement can occur across the peritoneal membrane (q_c). Alternatively, fluid movement can occur through the lymphatics or move directly

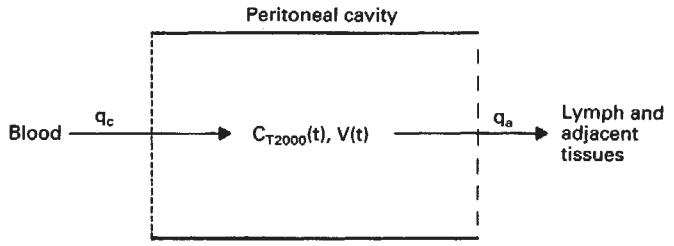

Fig. 1. *A schematic representation of fluid balance during a peritoneal exchange.* Dialysate volume V and the concentration of the index solute C_{T2000} are dependent on dwell time because of fluid movement into and out of the peritoneal cavity. Two different pathways of fluid movement are represented by q_c and q_a.

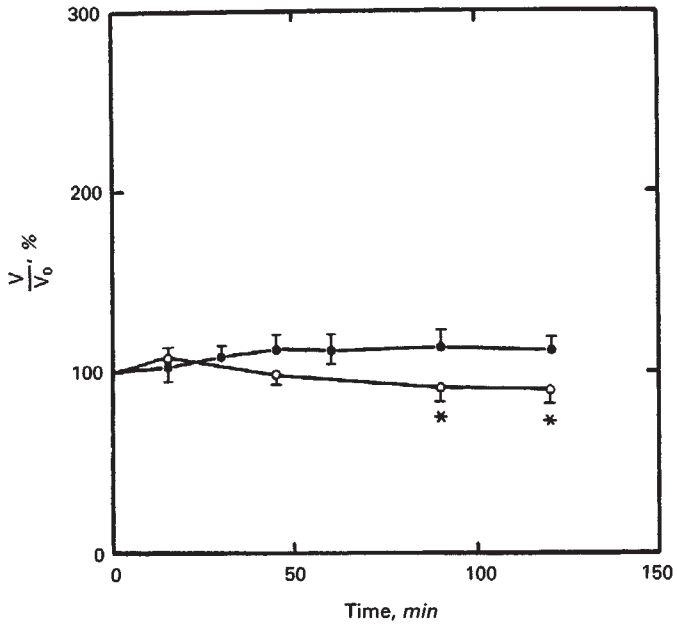

Fig. 2. *The dependence of dialysate volume relative to the initial infused volume V/V_0 as determined by SIIS using the concentration of dextran T2000 (solid circles) and MIIS using the concentration of the Evans blue-albumin complex (open circles) during the isotonic exchange.* Results are shown from 12 experiments, and the single asterisk denotes a significant difference where $P < 0.05$.

into adjacent tissues (q_a). These two pathways can be distinguished by the size of solutes that accompany the fluid movement. The former pathway (q_c) is assumed to restrict the transport of all macromolecules, whereas the latter (q_a) is assumed not to hinder the transport of macromolecules to any measurable extent. Depending upon the osmotic composition of the peritoneal dialysis solution, q_c may be either positive (into the cavity) or negative (out of the cavity).

Using assumptions regarding the nature of the above pathways and the technique of a typical experiment, it is shown in the Appendix that the values of q_c and q_a can be calculated from simultaneous estimates of V_{T2000} and V_{EB} by the following equations

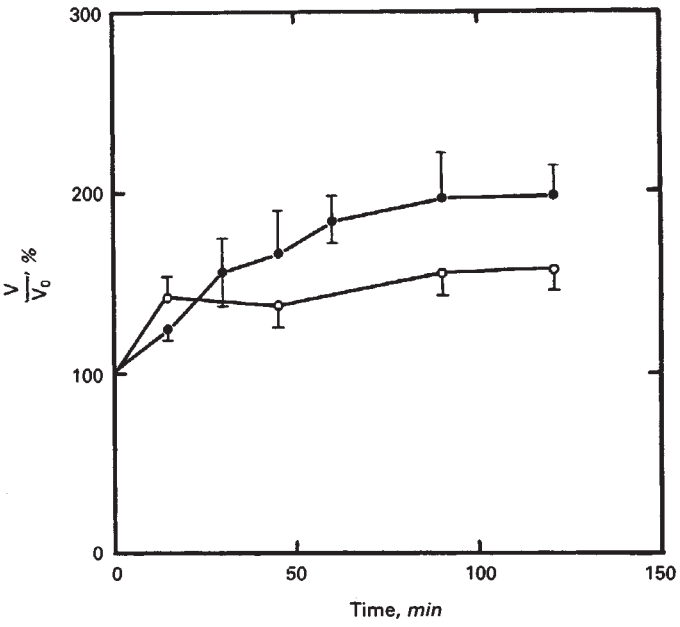

Fig. 3. *The dependence of dialysate volume relative to the initial infused volume V/V_0 as determined by SIIS (solid circles) and MIIS (open circles) during the hypertonic exchange.* Results are shown from 5 experiments, and no significant differences were noted.

$$q_c = \frac{V_{EB}(t_2) - V_{EB}(t_1)}{t_2 - t_1} \frac{\ln[V_{T2000}(t_2)/V_{T2000}(t_1)]}{\ln[V_{EB}(t_2)/V_{EB}(t_1)]} \quad (3)$$

$$q_a = q_c - \frac{V_{EB}(t_2) - V_{EB}(t_1)}{t_2 - t_1} \quad (4)$$

where ln is the natural logarithm. The estimates of q_c and q_a are for the interval between the sampling times t_2 and t_1.

Statistics

All results are described as the mean value ± the standard error of the mean (SEM). All paired statistical comparisons between volume determinations were performed only when they were simultaneously available.

Results

The volumes of peritoneal dialysis solution relative to the initial infused volume V_0 as a function of dwell time as determined by both the SIIS and MIIS methods are shown in Figures 2, 3, and 4 for the isotonic, hypertonic, and hypotonic solutions, respectively. The results shown in these figures include experiments with both catheters A and B. The volumes determined by either method are in qualitative agreement with expected findings based upon the initial osmolalities of the dialysis solutions. When using isotonic dialysis solution (302 ± 2 mOsm/kg H_2O), dialysate volume was relatively constant during the 120 minute dwell. The use of hypertonic dialysis solution (567 ± 15 mOsm/kg H_2O) resulted in a continuously increasing volume. These results are similar to those we have reported previously using the SIIS method [4]. Hypotonic dialysis solution (81 ± 15 mOsm/kg H_2O) resulted in the loss of fluid, the magnitude of the volume decrease depending dramatically upon

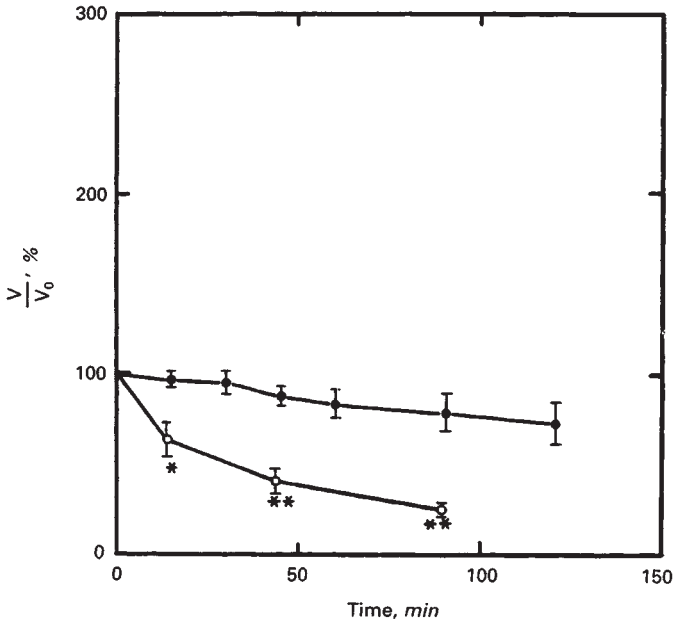

Fig. 4. *The dependence of dialysate volume relative to the initial infused volume V/V_0 as determined by SIIS (solid circles) and MIIS (open circles) during the hypotonic exchange.* Results are shown from 5 experiments. A single asterisk denotes a significant difference where $P < 0.05$, and a double asterisk denotes a significant difference where $P < 0.01$.

Table 1. Dialysate volumes determined by drainage and by the MIIS method at the end of the isotonic exchange using either catheter A or B

Catheter type	Drained volume	MIIS volume
A ($N = 4$)	71 (3)[a]	100 (7)[a]
B ($N = 8$)	87 (8)	89 (8)

Values are shown in ml, and the SEM is shown in parentheses.
[a] Significantly different as determined by a paired t-test ($P < 0.05$)

the method for determining dialysate volume. During the isotonic exchange, a comparison of the volumes determined by SIIS versus MIIS at each time using a paired t-test showed significant differences only at 90 and 120 minutes. At these latter times the volume determined by the SIIS method was higher than that determined by MIIS. Except at 15 minutes of dwell time, dialysate volumes determined by the SIIS method were larger than those determined by MIIS during the hypertonic exchange. None of the observed differences during the hypertonic exchange however reached statistical significance. During the hypotonic exchange, dialysate volumes determined by SIIS were significantly higher than those determined by MIIS at each time studied.

Catheter A was used in the first four experiments, but catheter B was used in the remainder. Table 1 shows the volumes estimated by drainage and by MIIS with both catheters A and B at the end of the isotonic exchange. The drained volume was significantly less than determined by MIIS when using catheter A but not when using catheter B.

A comparison of the volumes determined by drainage using catheter B, by MIIS, and by SIIS at the end of the exchange for all three different dialysis solutions is shown in Table 2. Analysis of variance with repeated measures [10] demonstrated significant differences between the three methods during the isotonic and hypotonic exchanges but not during the hypertonic exchange. The drained volume was significantly lower than that determined by SIIS during the isotonic exchange. During the hypotonic exchange, the volume determined by SIIS was significantly higher than for both the drained volume and the volume determined by MIIS.

Table 2. Dialysate volumes determined at the end of the exchange by drainage using catheter B, by MIIS using the concentration of the Evans blue-albumin complex, and by SIIS using the concentration of dextran T2000

Exchange osmolality	Drained volume	MIIS volume	SIIS volume
Isotonic ($N = 7$)	83 (8)[a]	86 (9)	121 (10)
Hypertonic ($N = 5$)	172 (9)	165 (22)	216 (22)
Hypotonic ($N = 5$)	33 (9)[a]	30 (2)[a]	95 (17)

All values are in ml, and the SEM is shown in parentheses. Significant differences between the volume estimates were found during the isotonic ($P < 0.05$) and hypotonic ($P < 0.01$) exchanges by analysis of variance with repeated measures.
[a] Significantly different from the SIIS volume as determined by a paired t-test using modified Bonferroni confidence limits ($P < 0.05$)

Table 3. Distribution volumes of injected Evans blue-albumin complex relative to the mean volume determined at 10 minutes shown as function of dwell time

Time *min*	Mean	Median
1/2	0.41 (0.06)	0.36
1	0.55 (0.06)	0.55
2	0.87 (0.09)	0.94
5	1.01 (0.08)	1.03
10	1.00 (0.09)	1.03

The releative mean value is shown, and the SEM is shown in parentheses ($N = 10$). The relative median value is also shown.

Systematic errors in dialysate volume measurements, in addition to loss of index solute from the peritoneal cavity, could potentially occur from two additional factors. First, the drained volume may be an underestimate of dialysate volume due to a substantial residual volume remaining in the peritoneal cavity. The residual fluid volume that could be aspirated on autopsy was small however. The residual volumes measured were 4 ± 1 ml ($N = 5$) and 1 ± 1 ml ($N = 5$) in the experiments using catheter B with the hypertonic and hypotonic dialysis solutions, respectively. Second, the distribution volume of newly injected Evans blue-albumin complex may not equal the volume of dialysis solution because of inadequate mixing. Table 3 shows the results from the experiments designed to test the degree of mixing of Evans blue-albumin complex as a function of dwell time after its injection into the peritoneal cavity. In this table the mean, SEM and median volumes of distribution calculated by using equation (2) are shown relative to the mean volume calculated at 10 minutes. Analysis of variance with repeated measures demonstrated a significant difference in the distribution volumes over this time range. When only those results at 2,

Table 4. The value of q_c and q_c' as calculated by equations (3) and (5), respectively, as a function of time during the isotonic, hypertonic and hypotonic exchange from the mean volumes shown in Figures 2-4

Time interval	Isotonic	Hypertonic	Hypotonic
$q_c/V_0 \times 10^3$			
0–15 min	1.9	18.9	−1.2
15–45 min	3.3	13.5	−1.7
45–90 min	0.2	5.5	−0.8
90–120 min	−0.6	0.2	
$q_c'/V_0 \times 10^3$			
0–15 min	1.9	16.7	−1.8
15–45 min	3.5	13.9	−3.1
45–90 min	0.3	6.8	−2.0
90–120 min	−0.8	0.3	

The values are normalized by the initial infused volume V_0 and have units of min^{-1}

5 and 10 minutes were considered, however, no significant differences were noted.

Table 4 shows the estimates of q_c relative to the initial infused volume V_0 for the appropriate time intervals using the simultaneous estimates of V_{T2000} and V_{EB} shown in Figures 2 through 4 and equation (3). Also shown in this table are estimates of the ultrafiltration rate across the peritoneal membrane q_c' relative to the initial infused volume estimated by simply calculating the change in volume as determined by SIIS, or

$$q_c' = \frac{V_{T2000}(t_2) - V_{T2000}(t_1)}{t_2 - t_1} \quad (5)$$

Only the mean volumes in Figures 2 through 4 were used so no error estimates are shown. The values of q_c show a small ultrafiltration rate into the peritoneal cavity during the isotonic exchange. The ultrafiltration rate is maximal during the hypertonic exchange at the beginning but decreases with dwell time. The low ultrafiltration rate near the end of the hypertonic exchange is consistent with the final measured dialysate osmolality of 318 ± 6 mOsm/kg H_2O. These calculations produce results qualitatively similar to those previously reported [2, 11]. The ultrafiltration rate during the hypotonic exchange is in the direction from the peritoneal cavity to plasma and does not decrease substantially with dwell time. Note that the values of q_c' using the more simple expression given in equation (5) are very similar to those using equation (3).

The values of q_a relative to the initial infused volume V_0 calculated from equation (4) were scattered and did not show a clear dependence on time. The values of q_a/V_0 (in min^{-1}) were therefore averaged over time to yield 1.6 ± 1.7 × 10^{-3}, 2.8 ± 4.2 × 10^{-3}, and 4.8 ± 1.1 × 10^{-3} during the isotonic, hypertonic, and hypotonic exchanges, respectively. The hypotonic value is larger but not different from either the isotonic or the hypertonic value.

Discussion

Recent clinical studies that have determined dialysate volume changes during peritoneal dialysis have revealed significant differences between the volumes determined by drainage and those by the conventional indicator dilution technique [5–7]. Volumes determined by drainage are subject to variable errors resulting from an inability to completely drain the peritoneal cavity. Thus, the drained volume is an underestimate of the volume of dialysis solution. On the other hand, the method for determining dialysate volume by conventional indicator dilution (SIIS) requires that the index solute not leave the peritoneal cavity, an assumption that is violated in practice. Fluid that is lost from the peritoneal cavity through the lymphatics and into adjacent tissues carries with it the index solute. Thus, fluid volume is lost without a change in concentration of the index solute leading to an overestimate of dialysate volume when calculated by this technique. The magnitude of these errors when determining dialysate volume has not been ascertained heretofore.

In this rabbit model of peritoneal dialysis we previously reported that drained volumes were substantially lower than expected, suggesting a relatively large residual volume after drainage [4]. The first four experiments in the present study were performed with the catheter previously employed, catheter A, and the remainder with catheter B. The volumes drained using catheter B were greater than those using catheter A and were not significantly different from those calculated using MIIS. Such results suggest that the volume remaining in the peritoneal cavity after drainage by catheter B is negligibly small. Indeed, small residual volumes (≤5 ml) were confirmed by direct measurement of the volume of dialysis solution remaining in the peritoneal cavity on autopsy. One interpretation would be to ascribe these observed differences in catheter drainage as being entirely due to catheter design. Catheter placement is also quite different between catheters, however, with catheter B lying in a more dependent portion of the abdominal cavity. There is the additional possibility that the increased experience of the experimenter with time also played a role in the differences noted. Nevertheless, these results demonstrate that the volume determined by drainage is expected to be sensitive to numerous variables between laboratories and may not be a reliable estimate of peritoneal dialysate volume.

Theoretically, the accuracy of the conventional indicator dilution technique could be improved if the index solute loss rate from the peritoneal cavity could be estimated. Clinical studies of peritoneal dialysis have employed the rate of index solute appearance in the blood stream to estimate solute loss from the peritoneal cavity [2, 8], but recent work has demonstrated that this approach does not accurately account for the total solute lost from the peritoneal cavity [5]. Indeed, Flessner et al have recently shown in the rat [12] that 90 to 97% of the fibrinogen that was lost from the peritoneal cavity was not recovered in the blood stream and had been distributed into the tissues surrounding the peritoneal cavity. Furthermore, the recent study of CAPD patients by Rippe et al [13] showed that the peritoneal disappearance rate for albumin was five times that for its appearance in plasma. Thus, corrections for the loss of index solute from the peritoneal cavity by that appearing in plasma may not be correct.

To minimize the importance of index solute loss, we have performed multiple indicator dilution measurements where the time for distribution of the index solute into the lymphatics and adjacent tissue spaces was limited to two minutes. The volumes determined by this technique as a function of dwell time are lower than when using SIIS, and the volumes at the end of the

exchange are not significantly different from those resulting from direct drainage of the peritoneal cavity using catheter B. One should not infer from these observations that the Evans blue-albumin complex does not leave the peritoneal cavity; indeed, on autopsy the tissues surrounding the peritoneal cavity are clearly stained blue. It appears, however, that the loss rate of index solute from the peritoneal cavity is small during a two minute dwell period.

One concern with our choice of a short dwell period when implementing the MIIS method is the distribution volume of the newly injected solute. Our experimental results (Table 3) demonstrate that mixing of the Evans blue-albumin complex is almost complete at two minutes and not significantly improved by extending the interval to 5 or 10 minutes. Although no statistical differences were noted, the mean and median data suggest potential systematic errors of 13% and 6%, respectively. In the present experiments a two minute dwell period was chosen as a compromise between mixing concerns and the alternative needs to measure rapid changes in dialysate volume as well as the abovementioned concern over index solute loss from the peritoneal cavity. In future experiments, especially with longer time intervals between samplings, a five minute dwell period may prove more accurate than the two minute period employed herein. Thus, the direct extrapolation of the technical findings described in this study is not recommended without experimental validation as there may be important differences in catheter function, in experimental design, in the animal model and in the presence of the uremic state. Nevertheless, the MIIS approach appears to offer a technique for accurately determining dialysate volume as a function of time during a peritoneal exchange.

The determination of dialysate volume by MIIS also has additional disadvantages however. The technique requires the frequent addition and removal of samples that would need for reasons of sterility to be performed with care in the clinic. Moreover, the volumes determined by this technique are quite variable although not much more so than those determined by SIIS. The increased variability when using MIIS results primarily from the need to accurately measure a difference in the index solute concentration (equation 2). The amount of added index solute required for the optimal application of this technique depends not only on several technical considerations, such as the number of determinations required and instrument sensitivity, but also on an estimate of dialysate volume. For example, in the present study a fixed amount of the Evans blue-albumin complex independent of dialysate volume was added to the peritoneal cavity. Therefore, volumes determined during the hypertonic exchange were more variable than those determined during the isotonic and hypotonic exchanges where dialysate volume was smaller and concentration changes of the index solute were more pronounced. This effect may be responsible for the lack of statistical difference between the volumes measured by MIIS and SIIS during the hypertonic exchange.

The model described schematically in Figure 1 and mathematically in the Appendix permits the calculation of fluid movement rates into and out of the peritoneal cavity. As expected, the calculated rates of fluid movement from blood into and out of the cavity (q_c) are determined by the osmolality of the dialysis solution. During the hypertonic exchange, there is a rapid influx of fluid into the peritoneal cavity that decreases with time as the osmolality of the dialysate approaches that of plasma. During the hypotonic exchange, however, fluid movement out of the peritoneal cavity is relatively constant, and the hypotonic dialysis solution did not quite reach osmotic equilibrium with plasma even after 120 minutes. It is of interest that the calculation of the ultrafiltration rate across the peritoneal membrane is well approximated by the simpler equation [5]. This is primarily because the loss of fluid by the lymphatics and into adjacent tissues does not result in a change of the index solute concentration. Thus, while the conventional indicator dilution technique is not accurate for determining dialysate volume, the change in concentration of the index solute (SIIS method) does provide a useful approach for estimating the ultrafiltration rate across the peritoneal membrane.

The present model also permits an estimation of the rate of fluid loss through the lymphatics and into adjacent tissues (q_a). It should be emphasized that q_a estimates the sum of both the lymphatic flow rate and that into adjacent tissue spaces. Although the values of q_a computed in the present study were scattered, they are in general agreement with recent estimates of this rate in the rat and in man when scaled to body weight to the 0.7 power. For example, the value of q_a during the isotonic and hypertonic exchanges averaged 0.24 ml/min (109 ml $\times$ 2.2 $\times$ 10^{-3} min^{-1}). This compares favorably with the rates of fluid movement out of the peritoneal cavity, as estimated using macromolecular tracer loss, by Flessner et al of 0.22 ml/min (35 μl/min $\times$ $(2.7/0.2)^{0.7}$) in the rat [12] and by Rippe et al of 0.09 ml/min (5 $\times$ 11.1 ml/hr $\times$ $(2.7/70)^{0.7}$) in man [13]. The need for considering fluid and solute transport by this pathway is demonstrated in these calculations since values of q_a are of the same order of magnitude as q_c.

We conclude that dialysate volumes measured by drainage are subject to errors of incomplete collection and additionally suffer from the disadvantage that they can only offer a value for the volume at the end of an exchange. The volumes obtained with the conventional indicator dilution technique (SIIS) can be greater than those determined by a multiple indicator dilution technique (MIIS) because of the loss of the index solute from the peritoneal cavity. Lastly, the use of other than isotonic dialysate can result in the exaggeration of differences between volumes determined by single and multiple injection of index solutes.

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Appendix

To examine the effect of index solute loss from the peritoneal cavity on the volume calculated by the conventional indicator dilution technique (SIIS) method, we consider a schematic model of the peritoneal cavity as shown in Figure 1. We assume that a volume of dialysis solution containing a known concen-

tration of the index solute was infused into the peritoneal cavity. We neglect any considerations of residual volume. Fluid transfer into or out of the peritoneal cavity can occur by two different pathways that can be distinguished by whether the index solute accompanies the fluid movement. The transfer of fluid across the peritoneal membrane occurs at a rate q_c and does not allow the simultaneous transfer of the index solute. On the other hand, fluid movement through the lymphatics or directly into adjacent tissue spaces occurs at a rate q_a, and this bulk flow of water contains the index solute at a concentration equal to that in the dialysis solution. With these assumptions, fluid and mass balance considerations lead to the following differential equations

$$\frac{dV}{dt} = q_c - q_a \tag{A1}$$

$$\frac{d(VC_{T2000})}{dt} = -q_a C_{T2000} \tag{A2}$$

where V and C_{T2000} are the true dialysate volume and the concentration of the index solute as a function of time. We have assumed that the index solute is dextran T2000.

If we assume that within the time interval of interest $t_2 - t_1$ the rate of fluid movement by the two pathways can be considered constant, equations (A1) and (A2) can be solved for V and C_{T2000}

$$V(t_2) = V(t_1) + (q_c - q_a)(t_2 - t_1) \tag{A3}$$

$$\frac{C_{T2000}(t_2)}{C_{T2000}(t_1)} = \left[\frac{V(t_1)}{V(t_2)}\right]^{\frac{q_c}{q_c - q_a}} \tag{A4}$$

The volume estimated using the index solute concentration (SIIS method) can be calculated by substituting equation (A4) into equation (1) of the main text

$$\frac{V_{T2000}(t_1)}{V_{T2000}(t_2)} = \left[\frac{V(t_1)}{V(t_2)}\right]^{\frac{q_c}{q_c - q_a}} \tag{A5}$$

Taking the logarithm of both sides of equation (A5) yields

$$(q_c - q_a)\ln[V_{T2000}(t_1)/V(_{T2000}(t_2)] = q_c \ln[V(t_1)/V(t_2)] \tag{A6}$$

Equation (A3) can then be solved for $q_c - q_a$

$$q_c - q_a = \frac{V(t_2) - V(t_1)}{t_2 - t_1} \tag{A7}$$

which when substituted into equation (A6) yields the following expression for q_c

$$q_c = \frac{V(t_2) - V(t_1)}{t_2 - t_1} \frac{\ln[V_{T2000}(t_2)/V_{T2000}(t_1)]}{\ln[V(t_2)/V(t_1)]} \tag{A8}$$

An expression for q_a can be obtained by rearranging equation (A7)

$$q_a = q_c - \frac{V(t_2) - V(t_1)}{t_2 - t_1} \tag{A9}$$

where q_c is first evaluated by equation (A8). Assuming that the true dialysate volume is determined by MIIS using Evans blue-albumin complex concentrations, equations (3) and (4) of the main text give the final result.

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